Total Synthesis of Guanacastepene A: A Route to Enantiomeric Control

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General Experimental Procedures

Commercial reagents were used without further purification unless otherwise indicated. Solvents were degassed with Ar and purified on a solvent drying system as described in Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520 unless otherwise indicated. Triethylamine (Et₃N), pyridine (py), and trimethylsilylchloride (TMSCl) were distilled from CaH₂ under N₂. Hexamethylphosphoramide (HMPA, (Me₂N)₃P=O) was distilled from CaH₂ and stored over 4Å MS. Reactions were performed in flame- or oven-dried glassware under positive Ar pressure with stirring by a magnetic stirbar unless otherwise indicated. Cold baths were generated as follows: 0 °C, wet ice/water; -44 °C, dry ice/CH₃CN; -78 °C, dry ice/acetone. Flash chromatography was performed on E. Merck 60 230-400 mesh silica gel. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized by UV (254 nm) and cerium ammonium molybdenate. IR spectra were recorded on an FTIR spectrometer with peaks reported in cm⁻¹. NMR spectra were recorded at 24 °C unless otherwise indicated. Chemical shifts are expressed in ppm relative to TMS (¹H, 0.00 ppm) or residual CDCl₃ (¹³C, 77.0 ppm). Peak assignments were made on the basis of J-RES, COSY, NOESY, DEPT, HMQC, and HMBC experiments. ¹H notations: m = multiplet, obsc = obscured, app = apparent. ¹³C DEPT notations: q = quaternary C, e = CH₂, o = CH or CH₃. H_a and H_b indicate stereochemistry not determined. H_α and H_β indicate stereochemistry as drawn. Atom numbering in structures is based on the numbering system for guanacastepene A with additional groups assigned arbitrary numbers above 22. Low resolution mass spectra were obtained by electrospray (ESI) ionization. High resolution mass spectra were obtained by fast atom bombardment (FAB) ionization.

Experimental and spectral data of compounds:

Keto-olefin 9. A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle was charged with a solution of **7** (0.429 g, 2.0 mmol) in 15 mL of THF and cooled at 0 °C while a solution of methyllithium–lithium iodide (1.0 M in ether, 2.1 mL, 2.1 mmol) was added rapidly dropwise by syringe. The resulting solution was stirred for 1 h, then cooled at –78 °C while a solution of 5-iodo-1-pentene (**8**) (0.98 g, 5.0 mmol) in 5 mL of hexamethylphosphoramide (HMPA) was added rapidly by syringe. The resulting slurry was allowed to stir overnight (17 h) with gradual warming to room temperature to give a yellow solution, which was diluted with 45 mL of ether and washed with three 10-mL portions of water and 10 mL of saturated NaCl solution. The organic layer was then dried over MgSO₄, filtered, and concentrated to give 0.93 g of a faintly yellow liquid. Purification by column chromatography on 42 g of silica gel (elution with 5% ether in pentane) provided 0.267 g (63%) of **9** as a colorless oil. Spectral data for **9** was consistent with that reported previously for this compound.

α -Chloro ketone 11. A 15-mL, one-necked, pear-shaped flask was charged with a mixture of **9** (0.104 g, 0.50 mmol), water (0.5 mL), chloramine-T (0.282 g, 1.0 mmol), and 0.5 mL of acetone. Sulfuric acid (3.0 M in water, 0.25 mL, 0.75 mmol) was added dropwise, and the resulting mixture was heated at 50 °C for 30 min, then cooled to room temperature and diluted with 2.5 mL of acetone. A mixture of CrO₃ (0.50 g, 5.0 mmol) and H₂SO₄ (3.0 M in water, 2.5 mL, 7.5 mmol) (Jones reagent) was then added, and the resulting orange–brown mixture was stirred for 30 min at room temperature before isopropanol (1.0 mL, 13 mmol) was added. After an additional 30 min, the reaction mixture was diluted with 20 mL of water and extracted with three 10-mL portions of ethyl acetate. The combined organic layers were washed with 10 mL of saturated NaCl solution, dried over MgSO₄, filtered, and deposited onto 0.39 g of silica gel. Purification by column chromatography on 13 g of silica gel (elution with 10% ethyl acetate in hexanes) provided 82 mg (63%) of **11** as a colorless oil: **IR** (thin film) 2962, 1734, 1458, 1405, 1170, 1087, and 956 cm^{–1}; **¹H NMR** (400 MHz, CDCl₃) δ 4.06 (s, 2H), 2.53–2.61 (m, 2H), 2.33–2.40 (m, 1H), 2.00–2.14 (m, 2H), 1.64–1.81 (m, 4H), 1.43–1.57 (m, 2H), 1.14–1.22 (m, 1H), 1.02 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), and 0.89 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 224.1, 202.3, 52.0, 48.1, 48.0, 40.0, 37.5, 36.5, 29.4, 23.7, 22.0, 21.4, 18.9, and 18.2. **HRMS** Calcd for C₁₄H₂₃ClO₂: 258.1387. Found: 259.1466 (M+H⁺).

β-Ketophosphonate 12. A 15-mL, one-necked, pear-shaped flask equipped with an argon inlet was charged with a solution of **11** (55 mg, 0.21 mmol) in 2 mL of acetone, and NaI (95 mg, 0.63 mmol) was added. The resulting mixture was stirred in the dark for 15 min, then was partitioned between 10 mL of ether and 2 mL of water. The organic layer was washed with 2-mL portions of 1 M Na₂S₂O₃ solution, water, and saturated NaCl solution, dried over MgSO₄, filtered, and concentrated (protected from light) to give 75 mg colorless oil, which was immediately dissolved in 5 mL of benzene in 25-mL, one-necked, pear-shaped flask equipped with a reflux condenser with an argon inlet. Triethyl phosphite (55 μL, 0.32 mmol) was added, and the resulting solution was heated at reflux for 5 h in the dark and then cooled to room temperature and concentrated to give 89 mg of a colorless oil. Purification by column chromatography on 8 g of silica gel (gradient elution with 50–100% ethyl acetate in hexanes) provided 56 mg (74%) of **12** as a colorless oil: **IR** (thin film) 3476, 2963, 1732, 1460, 1406, 1369, 1256, 1164, 1025, 967, and 800 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 4.14 (apparent quint, *J* = 7.0 Hz, 4H), 3.05 (d, *J*_{H-P} = 22.7 Hz, 2H), 2.51–2.63 (m, 2H), 2.31–2.40 (m, 1H), 2.00–2.12 (m, 2H), 1.78–1.84 (m, 1H), 1.62–1.72 (m, 3H), 1.42–1.50 (m, 2H), 1.34 (t, *J* = 7.0 Hz, 6H), 1.13–1.20 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H), and 0.88 (s, 3H); **¹³C NMR** δ 224.2, 201.7 (d, *J*_{C-P} = 6.1 Hz), 62.5 (m), 52.0, 48.0, 44.3, 42.3 (d, *J*_{C-P} = 127.3 Hz), 37.6, 36.6, 29.4, 23.7, 22.0, 21.5, 18.8, 18.2, and 16.3 (d, *J*_{C-P} = 6.1 Hz); **ESIMS** *m/z* 361.4 (M+H⁺, C₁₈H₃₃O₅P requires 361.4).

[5,5]-Bicyclic enone 14. A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser with an argon inlet was charged with **12** (42 mg, 0.11 mmol), Cs₂CO₃ (0.19 g, 0.58 mmol), and 22 mL of toluene, and the resulting mixture was heated at reflux for 12 h, then cooled to room temperature. The liquid was decanted, washed with 5 mL of water and 5 mL of saturated NaCl solution, dried with MgSO₄, filtered, and concentrated. Purification by column chromatography on 5 g of silica gel (elution with 10% ethyl acetate in hexanes) provided 21 mg (83%) of **14** as a colorless oil. Spectral data for **14** was consistent with that reported previously for this compound.

Diiodide 16. A 500-mL, one-necked, round-bottomed flask equipped with an argon inlet was charged with a mixture of triphenylphosphine (14.69 g, 56 mmol), imidazole (3.81 g, 56 mmol), and 150 mL of CH_2Cl_2 and immersed in a room temperature water bath. The stirred mixture became homogeneous within 5 min, at which time iodine (14.21 g, 56 mmol) was added. After an additional 10 min, a solution of **15** (7.9 g, 37 mmol) in 35 mL of CH_2Cl_2 was added. The resulting mixture was stirred for 1 h in the dark, then diluted with 185 mL of hexanes, filtered through Celite with the aid of three 50-mL portions of hexanes, and concentrated. Purification by column chromatography on 60 g of silica gel (elution with hexanes) provided 11.0 g (92%) of **16** as a colorless liquid: **IR** (thin film) 3062, 2934, 2835, 1608, 1425, 1305, 1280, 1263, 1198, 1164, and 691 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 6.30 (d, $J = 7.4\text{ Hz}$, 1H), 6.18 (apparent q, $J = 7.1\text{ Hz}$, 1H), 3.21 (t, $J = 7.0\text{ Hz}$, 2H), 2.27 (apparent q, $J = 7.2\text{ Hz}$, 2H), and 1.98 (apparent quint, $J = 7.2\text{ Hz}$, 2H); **^{13}C NMR** (100 MHz, CDCl_3) δ 139.0, 84.0, 35.6, 31.8, and 5.4.

Vinyl iodide 17. A 200-mL, one-necked, round-bottomed flask equipped with a rubber septum pierced with an argon inlet needle was charged with a solution of **7** (1.91 g, 9.0 mmol) in 66 mL of THF and cooled at $0\text{ }^\circ\text{C}$ while a solution of methyllithium–lithium iodide (0.93 M in ether, 9.8 mL, 9.1 mmol) was added rapidly dropwise by syringe. The resulting solution was stirred for 1 h, then cooled at $-78\text{ }^\circ\text{C}$ while a solution of **16** (7.22 g, 22 mmol) in 22 mL of hexamethylphosphoramide (HMPA) was added rapidly by syringe. The resulting slurry was allowed to stir overnight (14 h) with gradual warming to room temperature to give a yellow solution, which was diluted with 200 mL of ether and washed with three 40-mL portions of water and 40 mL of saturated NaCl solution. The organic layer was then dried over MgSO_4 , filtered, and concentrated to give a yellow oil. Purification by column chromatography on 75 g of silica gel (gradient elution with 2–5% ethyl acetate in hexanes) provided ca. 4.5 g of unreacted **16**, followed by 2.28 g (76%) of **17** as a colorless oil: **IR** (thin film) 2959, 2870, 1736, 1608, 1458, 1406, 1386, 1373, 1281, 1231, and 1080 cm^{-1} ; **^1H NMR** (400 MHz, CDCl_3) δ 6.20 (d, $J = 7.4\text{ Hz}$, 1H), 6.14 (apparent q, $J = 6.8\text{ Hz}$, 1H), 2.32–2.40 (m, 1H), 2.01–2.13 (m, 4H), 1.65–1.82 (m, 3H), 1.42–1.58 (m, 3H), 1.00–1.15 (m, 1H), 1.01 (d, $J = 6.4\text{ Hz}$, 3H), 0.95 (d, $J = 6.4\text{ Hz}$, 3H), and 0.90 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 224.1, 140.8, 82.7, 52.0, 48.2, 37.6, 36.9, 35.0, 29.4, 23.7, 23.3, 22.1, 21.5, and 18.3. **HRMS** Calcd for $\text{C}_{14}\text{H}_{23}\text{IO}$: 334.0794. Found: 335.0875 ($\text{M}+\text{H}^+$).

Allylic alcohol 18. A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet, a 250-mL pressure equalizing dropping funnel, and a rubber septum was charged with 150 mL of THF and cooled in a 0 °C bath. A solution of *n*-butyllithium (2.5 M in hexanes, 9.0 mL, 22.5 mmol) was added, followed immediately by dropwise addition of a solution of **17** (1.50 g, 4.5 mmol) in 150 mL of THF over 40 min. The resulting solution was stirred for 30 min, then was diluted with 50 mL of water and washed with two 50-mL portions of saturated NaCl solution. The combined aqueous solutions were extracted with 50 mL of ether, and the combined organic phases were dried over MgSO₄, filtered, and concentrated to give a wet orange oil. Purification by column chromatography on 93 g of silica gel (gradient elution with 2.5–10% ethyl acetate in hexanes) provided 0.15 g (16%) of **19**, followed by 0.580 g (62%) of **18** as a yellow oil: **IR** (thin film) 3616, 3468, 2956, 2879, 1458, 1376, 1013, and 704 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 5.59–5.69 (m, 2H), 2.23–2.42 (m, 1H), 2.03–2.18 (m, 2H), 1.65–1.82 (m, 4H), 1.32–1.62 (m, 6H), 0.99 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), and 0.86 (d, *J* = 6.5 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 137.6, 132.0, 83.3, 53.9, 49.1, 40.1, 39.7, 30.4, 30.2, 24.8, 23.0, 22.3, 19.4, and 17.5. **HRMS** Calcd for C₁₄H₂₄O: 208.1827. Found: 208.1818.

Hydroazulene 2. A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet was charged with 4.84 g of oven-dried, powdered 3Å molecular sieves, PCC (2.42 g, 11.2 mmol), and 19 mL of CH₂Cl₂. To this vigorously stirred suspension was added a solution of **18** (0.78 g, 3.7 mmol) in 18 mL of CH₂Cl₂, and the resulting brown mixture was stirred for 30 min at room temperature and then deposited onto 9.7 g of silica gel. Purification on 77 g of silica gel (elution with 10% ethyl acetate in hexanes) provided 0.550 g (71%) of **20** as a colorless oil: **IR** (thin film) 2956, 2870, 1652, 1464, 1426, 1366, 1336, 1260, 1191, 970, and 865 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 5.81 (apparent t, *J* = 1.7 Hz, 1H), 2.37–2.71 (m, 4H), 2.12 (ddd, *J* = 13.9, 7.2, and 3.5 Hz, 1H), 1.91–2.03 (m, 1H), 1.78–1.90 (m, 2H), 1.61–1.75 (m, 2H), 1.43–1.57 (m, 2H), 1.05 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), and 0.93 (d, *J* = 6.7 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 204.3, 171.9, 123.8, 58.6, 50.0, 44.2, 38.8, 32.9, 27.9, 25.6, 24.1, 22.0, 21.0, and 20.7. **HRMS** Calcd for C₁₄H₂₂O: 206.1671. Found: 206.1666.

Dideuterated vinyl iodide 17-d₂: Into a 25 mL round-bottomed flask, equipped with magnetic spin bar and argon filled balloon was taken **17** (182 mg, 0.54 mmol, azeotropically dried from toluene) in 4 mL CD₃OD. Freshly distilled triethyl amine (0.22 mL, 1.62 mmol, 3 equiv.) was added and the resulting solution was stirred for 16 hr at room temperature. Evaporation of the reaction mixture provided crude product, which was purified by silica gel column chromatography (3% ethyl acetate in hexanes) to afford mono deuterated compound in 94% yield. This mono deuterated compound was further dissolved in 4 mL CD₃OD and 100 μ L of DBU was added. The resulting solution was stirred for 4 hr at room temperature to obtain the dideuterated compound **17-d₂** in 91% yield. **¹H-NMR** (500 MHz, CDCl₃): δ 6.18 (d, J = 8 Hz, 1H), 6.13 (apparent q, J = 6.5 Hz, 1H), 2.06 (m, 3H), 1.79-1.64 (m, 3H), 1.52-1.40 (m, 3H), 1.07 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.0 Hz, 3H), 0.88 (s, 3H); **¹³C-NMR** (125 MHz, CDCl₃): δ 224.6, 141.2, 83.1, 52.4, 48.7, 37.3, 35.4, 29.8, 23.9, 23.8, 22.6, 21.9, 18.7.

12 β -Isopropyl-11 β -methyl-8-*exo*-methylene-($\Delta^{1,2}$)-hydroazulen-3-one 27. A solution of lithium hexamethyldisilazide (1.0 M in THF, 7.5 mL, 7.5 mmol, 1.5 equiv) and 12.5 mL of THF was cooled at -78°C in a 50-mL pear-shaped flask under argon. A solution of hydroazulene **20** (1.03 g, 5.0 mmol, 1.0 equiv) in 15 mL of THF was added dropwise over 5 min. The resulting solution was stirred for 1 h at -78°C , then transferred via cannula over 15 min to a stirred suspension of Eschenmoser's salt (2.28 g, 12.3 mmol, 2.5 equiv) in 15 mL of THF at -78°C under argon. (Note: the enolate solution flask is *not rinsed with additional solvent* during cannula transfer.) The resulting mixture was stirred for 10 min at -78°C , then for 10 min in a room temperature water bath, and then transferred to a separatory funnel with 50 mL of ether and 150 mL of saturated sodium bicarbonate solution. The aqueous layer was separated, diluted with 50 mL of water, and extracted with 50 mL of CH₂Cl₂. The combined organic layers were partially dried over Na₂SO₄, filtered, and concentrated at reduced pressure to give a wet, yellow-orange oil. This crude material was partitioned between 50 mL of CH₂Cl₂ and 25 mL of saturated sodium bicarbonate solution in a 200-mL round-bottomed flask, and *m*-CPBA (Aldrich, 57–86%, 2.27 g, 7.5–11.3 mmol, 1.5–2.3 equiv) was added in one portion. The resulting mixture was stirred vigorously for 20 min, then transferred to a separatory funnel and separated. The aqueous layer was extracted with 25 mL of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure *at room temperature* to give a crude, yellow oil. Purification by flash column chromatography on 109 g of silica gel (gradient elution with 5–10% ether/hexanes) provided 0.94 g of **27** (86%) as a pale yellow oil. **TLC:** R_f 0.32 (95:5 hexanes/EtOAc). **IR** (film): 2938.0, 1660.1, 1611.7, 1301.8. **¹H-NMR** (400 MHz, CDCl₃): δ 5.99 (app s, 1H), 5.91 (app d, 1H, J = 1.9 Hz), 5.27 (app s, 1H), 2.43-2.62 (m, 4H) 2.02-2.10 (m, 1H), 1.83-1.92 (m, 2H), 1.65 (hept, 1H J = 7.1 Hz), 1.31-1.49 (m, 2H),

1.02 (s, 3H), 0.99 (d, 3H, $J = 6.6$ Hz), 0.94 (d, 3H, $J = 6.6$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 195.6, 173.4, 148.1, 123.3, 121.7, 60.9, 49.7, 41.5, 34.8, 31.5, 28.9, 27.8, 24.8, 23.5, 22.9; **ESI-MS** m/z (rel int): (pos) 256.9 ($[\text{M}+\text{K}]^+$, 100), 241.0 ($[\text{M}+\text{Na}]^+$, 95), 219.1 ($[\text{M}+\text{H}]^+$, 55). **HRMS** (EI) m/z 219.1747 ($\text{M}+\text{H}^+$), calcd for $\text{C}_{15}\text{H}_{22}\text{O}$ 218.1671

8-Allyl-12 β -isopropyl-11 β -methyl-($\Delta^{1,2}$)-hydroazulen-3-one ($\Delta^{3,8}$)-trimethylsilyl enol ether

28. In a base-washed 100 mL round bottom flask, CuI (1.22 g, 6.42 mmol, 1.5 equiv) is suspended in 15.7 mL THF (Aldrich SureSeal) and cooled to -78 °C. Vinyl magnesium bromide (1.0 M in THF, 12.85 mL, 12.85 mmol, 3.0 equiv) is added slowly via syringe, then the flask transferred to a -44 °C bath and stirred for 45 min. Over this time, the reaction mixture turns from an orange-brown slurry to an olive-gray slurry. In a separate 100 mL conical flask, exo-methylene hydroazulenone **27** (935 mg, 4.28 mmol, 1.0 equiv) is azeotroped 1 $\times$ from PhH *at rt* then dissolved in 15 mL THF. Freshly distd TMSCl (2.45 mL, 19.27 mmol, 4.5 equiv) is added to the hydroazulenone via syringe and the solution is mixed for 2 min. The cuprate flask is cooled to -78 °C and HMPA (3.35 mL, 19.27 mmol, 4.5 equiv) is added via syringe. The hydroazulenone/TMSCl solution is cooled to -78 °C then transferred via canula to the cuprate flask with vigorous stirring. The hydroazulenone flask is rinsed 2 $\times$ 5 mL THF. The resulting olive slurry is stirred for 25 min at -78 °C, then freshly distd Et_3N (3.00 mL, 21.41 mmol, 5.0 equiv) is added via syringe. The flask is removed from the bath and allowed to warm to rt. The resulting black reaction mixture is cooled to 0 °C, quenched with 20 mL satd aq NH_4Cl (adjusted to pH 8 with NH_4OH), and allowed to warm to rt. The mixture is poured into 100 mL hexanes and more $\text{NH}_4\text{Cl}/\text{NH}_4\text{OH}$ solution is added. The layers are separated and the aq layer is extracted 2 $\times$ hexanes. The combined organic layers are washed 1 $\times$ $\text{NH}_4\text{Cl}/\text{NH}_4\text{OH}$, 1 $\times$ H_2O , 1 $\times$ brine, dried (Na_2SO_4), filtered, and evaporated to yield the crude trimethylsilyl enol ether **28** as a yellow oil (1.364 g, 100%, 95% purity by NMR). The crude product is best carried on directly to the next step, but can also be purified by silica flash chromatography (199:1 hexanes/ EtOAc , 64%). **TLC**: R_f 0.68 (9:1 hexanes/ EtOAc). **IR** (film): 3075, 2957, 2870, 1654, 1637, 1251, 1153, 902, 842, 753. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 5.77 (ddt, 1H, $J = 16.9, 10.1, 6.8$, C6-H), 5.46 (app t, 1H, $J = 1.8$ Hz, C2-H), 5.01 (app dq, 1H, $J = 17.0, 1.6$ Hz, C5-H $_Z$), 4.96 (dm, 1H, $J = 9.9$ Hz, C5-H $_E$), 2.85 (m, 2H, C7-H $_2$), 2.38 (m, 2H, C14-H $_2$), 2.17 (m, 2H, C9-H $_2$), 1.94 (dt, 1H, $J = 13.5, 5.1$ Hz, C10-H $_\beta$), 1.81 (m, 1H, C13-H $_\alpha$), 1.66 (app sxt, 1H, $J = 6.8$ Hz, C18-H), 1.46 (obsc m, 1H, C10-H $_\alpha$), 1.41 (obsc m, 1H, C13-H $_\beta$), 1.39 (ddd, 1H, $J = 12.8, 7.3, 5.7$ Hz, C12-H), 0.96 (d, 3H, $J = 6.7$ Hz, C19-H $_3$), 0.92 (d, 3H, $J = 6.7$ Hz, C20-H $_3$), 0.86 (s, 3H, C17-H $_3$), 0.16 (s, 9H, (C23-H $_3$) $_3$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ 157.1 (C1), 141.3 (C3), 137.1 (C6), 119.8 (C3), 117.8 (C2), 114.6 (C5), 58.2 (C12), 46.9 (C11), 38.1 (C10), 37.6 (C7), 32.3 (C14), 28.5 (C9, C18), 27.8 (C13), 23.7 (C19), 22.5 (C20), 15.7 (C17), 0.7 (C23 $_3$). **ESI-MS** m/z (rel int): (pos) 269.2 ($[\text{M}+\text{Na}]^+$, 100), 247.1 ($[\text{M}+\text{H}]^+$, 5).

8 β -Allyl-8 α ,11 β -dimethyl-12 β -isopropyl-($\Delta^{1,2}$)-hydroazulen-3-one 29. In a 50 mL conical flask, the crude silyl enol **28** (1.364 g, 4.28 mmol, 1.0 equiv) is azeotroped 2 $\times$ from PhH, then dissolved in 21.4 mL THF (Aldrich SureSeal) to form a light yellow solution which is cooled to 0 $^{\circ}$ C. Methyl lithium (1.3 M in Et₂O, 4.94 mL, 6.42 mmol, 1.5 equiv) is added via syringe and the orange brown solution is stirred for 10 min at 0 $^{\circ}$ C, then cooled to -78° C. HMPA (3.83 mL, 21.41 mmol, 5.0 equiv) then methyl iodide (1.33 mL, 21.41 mmol, 5.0 equiv) are added via syringe and the flask is removed from the bath and allowed to warm to rt. After 20 min, the reaction mixture is poured into satd aq NaHCO₃, diluted with H₂O to dissolve precipitated solids, then extracted 3 $\times$ Et₂O. The combined organic extracts are washed 1 $\times$ H₂O, 1 $\times$ brine, dried (MgSO₄), filtered, and evaporated to yield the crude product as a yellow liquid (1.120 g). Purification by silica flash chromatography (99:1 hexanes/EtOAc) yields 8 β -allyl-8 α -methyl hydroazulenone **29** as a clear oil (862 mg, 77% for two steps). **TLC:** *R_f* 0.29 (9:1 hexanes/EtOAc). **IR** (film): 3073, 2959, 2871, 1655 (C=O), 1465, 1378, 1232, 1001, 910. **¹H-NMR** (500 MHz, CDCl₃): δ 5.80 (app ddt, 1H, *J* = 15.4, 11.2, 7.6 Hz, C6-H), 5.68 (app t, 1H, *J* = 1.8 Hz, C2-H), 5.041 (obsc dm, 1H, *J* = 11.3 Hz, C5-H_E), 5.036 (obsc dm, 1H, *J* = 15.9 Hz, C5-H_Z), 2.52 (app ddt, 1H, *J* = 17.5, 8.3, 1.8 Hz, C14-H _{β}), 2.45 (app dd, 1H, *J* = 13.7, 6.8 Hz, C7-H _{β}), 2.36 (ddd, 1H, *J* = 18.4, 9.3, 1.7 Hz, C14-H _{α}), 2.19 (dd, 1H, *J* = 13.8, 7.9 Hz, C7-H _{α}), 2.01 (ddd, 1H, *J* = 14.7, 12.6, 2.1 Hz, C9-H _{β}), 1.93 (ddd, 1H, *J* = 14.4, 7.0, 2.1 Hz, C10-H _{β}), 1.87 (obsc m, 1H, C13-H _{α}), 1.85 (obsc m, 1H, C10-H _{α}), 1.66 (app oct, 1H, *J* = 6.7 Hz, C18-H), 1.49 (obsc m, 1H, C13-H _{β}), 1.47 (obsc m, 1H, C9-H _{α}), 1.44 (obsc m, 1H, C12-H), 1.13 (s, 3H, C16-H₃), 0.99 (d, 3H, *J* = 6.7 Hz, C19-H₃), 0.94 (s, 3H, C17-H₃), 0.91 (d, 3H, *J* = 6.7 Hz, C20-H₃). **¹³C-NMR** (125 MHz, CDCl₃): δ 208.2 (C3), 167.2 (C1), 135.4 (C6), 122.0 (C2), 117.4 (C5), 57.3 (C12), 49.8 (C8), 49.3 (C11), 43.7 (C7), 33.6 (C10), 32.0 (C14), 31.4 (C9), 28.0 (C18), 25.7 (C13), 24.8 (C16), 24.1 (C19), 22.0 (C20), 20.7 (C17). **ESI-MS** *m/z* (rel int): (pos) 283.1 ([M+Na]⁺, 50), 261.1 ([M+H]⁺, 5). **HRMS** (EI) *m/z* 261.2229 (M+H⁺), calcd for C₁₈H₂₈O 260.2140

8 α -Allyl-8 β ,11 β -dimethyl-12 β -isopropyl-($\Delta^{1,2}$)-hydroazulen-3-one 32: A 25-mL, round-bottomed flask equipped with a reflux condenser was charged with Wilkinson's catalyst (1 mg, 0.001 mmol, 0.01 equiv). A solution of enone **27** (0.01 M in benzene, 10 mL, 0.1 mmol, 1.0 equiv) was added, followed by dimethylphenylsilane (0.15 mL, 1.0 mmol, 10 equiv), and the resulting yellow solution was heated at reflux under argon. After 20 min, the reaction mixture was cooled to room temperature, diluted with 10 mL of toluene, and concentrated at reduced pressure. The resulting residue was filtered quickly through a plug of silica gel (elution with 10% ethyl acetate/hexanes) to afford 43 mg of an orange oil, which was used without further

purification in the next step. In a 10-mL pear-shaped flask, the crude enolsilane (43 mg) was dissolved in 1 mL of THF and cooled to 0 °C under argon. Methyllithium (1 M in ether, 0.3 mL, 0.3 mmol, 3 equiv) was added via syringe. After 15 min, the reaction mixture was cooled to -78 °C and treated with allyl iodide (91 μ L, 1.0 mmol, 10 equiv) and the reaction mixture was removed from the bath and allowed to warm to rt. After an additional 30 min, the reaction mixture was partitioned between ethyl acetate and half-saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered, concentrated under reduced pressure, and purified on 5.2 g of silica gel (elution with 2% ethyl acetate/hexanes) to provide 18 mg (69% overall) of ketone **32** as a colorless oil. **IR** (film): 2960, 2871, 1668 (C=O), 1456, 1375, 1198, 1118, 994, 913. **¹H-NMR** (500 MHz, CDCl₃): δ 5.65 (app s, 1H, C2-H), 5.63 (obsc m, 1H, C6-H), 5.04 (obsc dm, 1H, J = 9.1 Hz, C5-H_E), 5.02 (obsc dm, 1H, J = 16.1 Hz, C5-H_Z), 2.51 (dd, 1H, J = 18.5, 7.8 Hz, C14-H _{β}), 2.39 (m, 2H, C7-H _{α} , C14-H _{α}), 2.21 (dd, 1H, J = 13.5, 7.7 Hz, C7-H _{β}), 1.92 (obsc m, 1H, C10-H _{α}), 1.86 (m, 3H, C9-H _{β} , C10-H _{β} , C13-H _{α}), 1.65 (m, 2H, C18-H, C9-H _{α}), 1.47 (m, 2H, C12-H, C13-H _{β}), 1.07 (s, 3H, C16-H₃), 0.99 (d, 3H, J = 6.7 Hz, C19-H₃), 0.94 (s, 3H, C17-H₃), 0.91 (d, 3H, J = 6.6 Hz, C20-H₃). **¹³C-NMR** (100 MHz, CDCl₃): δ 209 (C3, by HMBC), 166.0 (C1), 133.5 (C6), 121.5 (C2), 118.0 (C5), 57.4 (C12), 50.7 (C8), 49.1 (C11), 42.8 (C7), 33.4 (C14), 32.8 (C10), 31.9 (C9), 27.9 (C18), 25.9 (C13), 24.1 (C19), 22.8 (C16), 22.0 (C20), 21.3 (C17). **ESI-MS** m/z (rel int): (pos) 283.1 ([M+Na]⁺, 60), 260.8 ([M+H]⁺, 100).

8 β -Allyl-8 α ,11 β -dimethyl-3,3-ethylenedioxy-12 β -isopropyl-($\Delta^{1,14}$)-hydroazulene 30. In a 100 mL round bottom flask, the 8-allyl-8-methyl hydroazulenone **29** (860 mg, 3.30 mmol, 1.0 equiv) is dissolved in 50 mL PhH. Ethylene glycol (5.53 mL, 99.1 mmol, 30 equiv) and TsOH $\cdot$ H₂O (314 mg, 1.65 mmol, 0.5 equiv) are added and the mixture is heated to reflux under a Dean-Stark condenser with vigorous stirring. After 36 h, the mixture is cooled to rt, then poured into satd aq NaHCO₃ and extracted 3 $\times$ Et₂O. The combined organic extracts are washed 2 $\times$ satd aq NaHCO₃, 1 $\times$ H₂O, 1 $\times$ brine, dried (MgSO₄), filtered, and evaporated to yield the crude product as a yellow oil (999 mg). Purification by silica flash chromatography (4:1 hexanes/CH₂Cl₂) yields the dioxolane as a clear oil (895 mg, 89%). **TLC**: R_f 0.39 (1:1 hexanes/CH₂Cl₂). **IR** (film): 2950, 2881, 1454, 1371, 1130, 1079 (C-O), 1010, 914. **¹H-NMR** (500 MHz, CDCl₃, partially assigned by COSY): δ 5.76 (dddd, 1H, J = 16.9, 10.2, 8.1, 6.7 Hz, C6-H), 5.36 (s, 1H, C14-H), 5.08 (obsc dm, 1H, J = 16.9 Hz, C5-H_Z), 5.06 (obsc dm, 1H, J = 9.9 Hz, C5-H_E), 4.02 (obsc m, 1H, C23/24-H), 3.96 (obsc m, 2H, C23/24-H, C23/24-H), 3.89 (obsc m, 1H, C23/24-H), 2.45 (dd, 1H, J = 14.0, 6.5 Hz, C7-H_a), 2.35 (obsc dm, 1H, J = 15.2 Hz, C2-H_a), 2.34 (obsc m, 1H, C13-H_a), 2.22 (obsc dd, 1H, J = 14.0, 8.2 Hz, C7-H_b), 2.20 (obsc d, 1H, J = 13.6 Hz, C2-H_b), 1.92 (ddm, 1H, J = 15.7, 9.9 Hz, C13-H_b), 1.73 (obsc m, 1H, C9/10-H), 1.69 (obsc m, 1H, C18-H), 1.65 (obsc m, 1H, C12-H), 1.44 (m, 2H, C9/10-H, C9/10-H), 1.17 (m, 1H, C9/10-H), 0.96 (d, 3H, J = 6.3 Hz, C19/20-H₃), 0.89 (s, 3H, C17/16-H₃), 0.88 (obsc d, 3H, J = 7.5 Hz, C20/19-H₃), 0.81 (s, 3H, C16/17-H₃). **¹³C-NMR** (100 MHz, CDCl₃): δ 147.1 (q), 135.2 (o), 126.4 (o), 117.5 (e), 112.8 (q), 65.1 (e), 64.5 (e), 54.0 (o), 49.7 (q), 44.6 (q), 38.3 (e), 35.5 (e), 32.4 (e), 32.1 (e), 29.7 (o), 29.3 (e), 23.1 (o), 22.9 (o), 21.0 (o), 20.7 (o). **ESI-MS** m/z (rel int): (pos) 327.1 ([M+Na]⁺, 30); (neg) 339.0 ([M+Cl]⁻, 50). **HRMS** (EI) m/z 305.2481 (M+H⁺), calcd for

C₂₀H₃₂O₂ 304.2402. In a 100 mL round bottom flask, the dioxolane (892 mg, 2.93 mmol, 1.0 equiv) is azeotroped 2 × from PhH then dissolved in 15 mL THF (Aldrich SureSeal) and cooled to 0 °C. A freshly prepared stock solution of 9-BBN (0.5 M in THF, 17.6 mL, 8.79 mmol, 3.0 equiv) is added via syringe and the reaction is removed from the bath and allowed to warm to rt. After 3.5 h, the mixture is cooled to 0 °C and NaOH (3 N aq, 9.67 mL, 29 mmol, 9.9 equiv) is added. H₂O₂ (30% aq, 2.99 mL, 29 mmol, 9.9 equiv) is added dropwise (*CAUTION! Evolves gas!*) then the mixture is allowed to warm to rt with vigorous stirring. The mixture is poured into 1 N aq NaOH and extracted 3 × Et₂O. The combined organic extracts are washed 1 × H₂O, 1 × brine, dried (MgSO₄), filtered, and evaporated to yield the crude product as a clear oil (1.879 g). Purification by silica flash chromatography (4:1 hexanes/EtOAc) yields the alcohol **30** as a clear viscous oil (927 mg, 98%). **TLC**: *R_f* 0.25 (2:1 hexanes/EtOAc). **IR** (film): 3432 (br, O–H), 2948, 2880, 1470, 1453, 1371, 1298, 1074 (C–O), 1002, 947. **¹H-NMR** (500 MHz, CDCl₃, partially assigned by COSY): δ 5.36 (s, 1H, C14-H), 4.03 (m, 1H, C23/24-H), 3.98–3.87 (m, 3H, C23/24-H, C23/24-H, C23/24-H), 3.67 (br s, 1H, C5-H), 2.36 (obsc dm, 1H, *J* = 12.8 Hz, C2-H_a), 2.35 (obsc m, 1H, C13-H_a), 2.18 (d, 1H, *J* = 13.5 Hz, C2-H_b), 1.92 (ddm, 1H, *J* = 15.7, 10.1 Hz, C13-H_b), 1.76–1.61 (m, 4H, C7/9/10-H, C18-H, C12-H, C7/9/10-H), 1.53–1.41 (m, 3H, C6-H_a, C7/9/10-H, C7/9/10-H), 1.32 (m, 2H, C6-H_b, C7/9/10-H), 1.18 (dd, 1H, *J* = 15.1, 8.5 Hz, C7/9/10-H), 0.96 (d, 3H, *J* = 6.3 Hz, C19/20-H₃), 0.88 (s, 3H, C17/16-H₃), 0.88 (obsc d, 3H, *J* = 6.1 Hz, C20/19-H₃), 0.83 (s, 3H, C16/17-H₃). **¹³C-NMR** (100 MHz, CDCl₃): δ 147.1 (q), 126.4 (o), 113.2 (q), 65.1 (e), 64.4 (e), 63.9 (e), 54.0 (o), 49.6 (q), 44.1 (q), 35.5 (e), 32.3 (e), 32.1 (e), 29.7 (o), 29.6 (e), 29.1 (e), 27.0 (e), 23.0 (o), 22.9 (o), 20.8 (o), 20.8 (o). **ESI-MS** *m/z* (rel int): (pos) 345.1 ([M+Na]⁺, 55), 319.1 ([M+H]⁺, 40); (neg) 356.9 ([M+Cl][–], 100). **HRMS** (EI) *m/z* 323.2586 (M+H⁺), calcd for C₂₀H₃₄O₃ 322.2508

8β-(3'-Carboxyethyl)-8α,11β-dimethyl-12β-isopropyl-(Δ^{1,14})-hydroazulen-3-one 31. In a 25 mL round bottom flask, the alcohol **30** (25.5 mg, 79.1 μmol, 1.0 equiv) is dissolved in 800 μL acetone (HPLC grade) and cooled to 0 °C under air. Freshly prepared Jones reagent (dissolve CrO₃ (790 mg, 7.91 mmol) in 3.95 mL 3 M aq H₂SO₄, then deliver 395 μL (791 μmol, 10 equiv CrO₃) of solution) is added to the alcohol and the reaction is stirred 40 min at 0 °C, then removed from the bath and allowed to warm to rt. The resulting orange slurry is quenched with 1 mL *i*-PrOH, forming a light green clear solution after 5 min. The mixture is poured into H₂O and extracted 3 × EtOAc. The combined organic extracts are washed 1 × H₂O, 1 × brine, dried (MgSO₄), filtered, and evaporated to yield the crude product as a white solid (25.3 mg). Purification by silica flash chromatography (85:15:1 hexanes/EtOAc/AcOH) yields the carboxy ketone **31** as a white solid (14.3 mg, 62%). **TLC**: *R_f* 0.18 (50:50:1 hexanes/EtOAc/AcOH). **mp** (uncorr): 135.7–137.3 °C. **IR** (film): 3500–2300 (br, COO–H), 2955, 1707 (C=O), 1462, 1423, 1379, 1294, 1266, 1213, 1073, 1044. **¹H-NMR** (500 MHz, CDCl₃): δ 5.44 (s, 1H, C14-H), 3.45 (br d, 1H, *J* = 11.6 Hz, C2-H_a), 2.96 (d, 1H, *J* = 11.7 Hz, C2-H_b), 2.36 (obsc ddd, 1H, *J* = 16.5, 10.6, 5.8 Hz, C6-H_a), 2.30 (obsc ddd, 1H, *J* = 16.4, 8.3, 2.9 Hz, C13-H_a), 2.23 (obsc ddd, 1H, *J* = 16.4, 10.6, 5.7 Hz, C6-H_b), 1.95 (obsc m, 2H, C9-H_a, C13-H_b), 1.90 (obsc m, 2H, C7-H_a, C10-H_a), 1.73 (m, 2H, C7-H_b, C18-H), 1.52 (obsc m, 1H, C9-H_b), 1.50 (obsc m, 1H, C12-H), 1.43 (app t, 1H, *J* = 12.8 Hz, C10-H_b), 1.05 (s, 3H, C16-H₃), 1.00 (s, 3H, C17-H₃), 0.97 (d, 3H, *J* = 6.5 Hz, C19-H₃), 0.88 (d, 3H, *J* = 6.6 Hz, C20-H₃). **¹³C-NMR** (100 MHz, CDCl₃): δ 212.3

(C3), 179.4 (C5), 143.6 (C1), 127.1 (C14), 58.3 (C12), 50.3 (C11), 49.6 (C8), 42.4 (C2), 36.6 (C10), 36.2 (C13), 34.7 (C7), 33.0 (C9), 30.0 (C18), 29.3 (C6), 23.5 (C19), 23.3 (C20), 21.0 (C16), 17.7 (C17). **ESI-MS** m/z (rel int): (pos) 315.1 ($[M+Na]^+$, 100); (neg) 326.9 ($[M+Cl]^-$, 35), 290.9 ($[M-H]^-$, 100).

8 β -(3'-Carboxyethyl)-8 α ,11 β -dimethyl-12 β -isopropyl-($\Delta^{1,14}$, $\Delta^{2,3}$)-hydroazulen-3-one dienol lactone **33.** In a 25 mL conical flask are placed the carboxy ketone **31** (13.2 mg, 45.1 μ mol, 1.0 equiv) and NaOAc (5.6 mg, 67.7 μ mol, 1.5), then 2.25 mL Ac_2O is added and the mixture is heated to reflux under a condenser for 80 min. The resulting light yellow cloudy solution is cooled to rt and the Ac_2O is evaporated. The residue is taken up in Et_2O , washed 1 $\times$ satd aq $NaHCO_3$, 1 $\times$ H_2O , 1 $\times$ brine, dried ($MgSO_4$), filtered, and evaporated to yield the crude product as a yellow oil (13.8 mg). Purification by silica flash chromatography (19:1 hexanes/ $EtOAc$) yields dienol lactone **33** as a clear oil (7.3 mg, 59%). **TLC**: R_f 0.52 (66:33:1 hexanes/ $EtOAc$ / $AcOH$), R_f 0.38 (4:1 hexanes/ $EtOAc$). **IR** (film): 2929, 1752 ($C=O$), 1451, 1341, 1246, 1212, 1167, 1102, 1080 ($C-O$), 880. **1H -NMR** (500 MHz, $CDCl_3$, partially assigned by COSY): δ 5.88 (s, 1H, C2-H), 5.51 (s, 1H, C14-H), 2.65 (ABX₂ obsc ddd, 1H, J = 17.6, 10.8, 6.5 Hz, C6- H_a), 2.59 (ABX₂ obsc ddd, 1H, J = 17.8, 6.5, 4.8 Hz, C6- H_b), 2.39 (2.39, 1H, J = 17.1, 7.8, 3.2 Hz, C13- H_a), 2.02 (ddm, 1H, J = 17.1, 10.3 Hz, C13- H_b), 1.94 (obsc m, 2H, C9/10-H, C9/10-H), 1.88 (obsc m, 1H, C7- H_a), 1.78 (obsc m, 1H, C18-H), 1.75 (obsc m, 1H, C9/10-H), 1.60 (obsc m, 1H, C12-H), 1.58 (obsc m, 1H, C7- H_b), 1.50 (dd, 1H, J = 14.4, 7.3 Hz, C9/10-H), 1.19 (s, 3H, C16/17- H_3), 1.00 (d, 3H, J = 6.5 Hz, C19/20- H_3), 0.95 (s, 3H, C17/16- H_3), 0.92 (d, 3H, J = 6.6 Hz, C20/19- H_3). **^{13}C -NMR** (100 MHz, $CDCl_3$): δ 169.1, 154.3, 145.7, 129.6, 108.6, 58.3 (br), 49.4 (br), 37.2, 35.9, 34.9, 34.0, 29.3, 27.4, 23.8, 23.3, 23.0, 17.9. **ESI-MS** m/z (rel int): (pos) 297.1 ($[M+Na]^+$, 95); (neg) 309.0 ($[M+Cl]^-$, 20).

8 α ,11 β -Dimethyl-3,3-ethylenedioxy-8 β -(2'-formylethyl)-12 β -isopropyl-($\Delta^{1,14}$)-hydroazulene **39.** In a 100 mL round bottom flask, the alcohol **30** (990 mg, 3.07 mmol, 1.0 equiv) is dissolved in 20 mL CH_2Cl_2 and cooled to 0 $^{\circ}C$. The Dess–Martin periodinane (Acros Organics, 15 wt% in CH_2Cl_2 , 13.2 mL, 4.60 mmol, 1.5 equiv) is added via syringe and the reaction mixture is removed from the bath and allowed to warm to rt during which time the clear solution becomes cloudy white. After 2 h, the reaction mixture is washed 1 $\times$ 1 N aq $NaOH$. The aq layer is back extracted 2 $\times$ CH_2Cl_2 and the combined organic layers are washed 1 $\times$ H_2O , 1 $\times$ brine, dried ($MgSO_4$), filtered, and evaporated to yield the crude product as a clear oil (939 mg). Purification by silica flash chromatography (9:1 hexanes/ $EtOAc$) yields aldehyde **39** as a clear oil (816 mg, 83%). **TLC**: R_f 0.52 (2:1 hexanes/ $EtOAc$). **IR** (film): 2950, 1726 ($C=O$), 1470, 1372, 1112, 1072 ($C-O$), 1011, 949. **1H -NMR** (500 MHz, $CDCl_3$): δ 9.81 (app t, 1H, J = 1.7 Hz, C5-H), 5.37 (s, 1H, C14-H), 4.04 (td, 1H, J = 6.6, 4.8 Hz, C23/24-H), 3.98 (td, 1H, J = 7.1, 4.7 Hz, C23/24-H), 3.94 (q, 1H, J = 7.0 Hz, C23/24-H), 3.88 (q, 1H, J = 6.8 Hz, C23/24-H), 2.48 (dddd,

1H, $J = 16.9, 11.4, 5.4, 1.6$ Hz, C6-H_a), 2.354 (obsc d, 1H, $J = 12.8$ Hz, C2-H_a), 2.345 (obsc m, 1H, C13-H_a), 2.32 (obsc dddd, 1H, $J = 16.8, 11.4, 5.4, 1.9$ Hz, C6-H_b), 2.20 (d, 1H, $J = 13.6$ Hz, C2-H_b), 1.92 (obsc m, 1H, C7-H_a), 1.88 (obsc m, 1H, C13-H_a), 1.85 (obsc m, 1H, C7-H_b), 1.74 (obsc dd, 1H, $J = 15.1, 8.4$ Hz, C10-H_a), 1.70 (obsc m, 1H, C18-H), 1.62 (obsc td, 1H, $J = 9.8, 7.7$ Hz, C12-H), 1.51 (dd, 1H, $J = 15.3, 11.6$ Hz, C9-H_a), 1.28 (dd, 1H, $J = 15.1, 11.5$ Hz, C10-H_b), 1.11 (dd, 1H, $J = 15.3, 8.4$ Hz, C9-H_b), 0.96 (d, 3H, $J = 6.4$ Hz, C19-H), 0.877 (obsc s, 3H, C17-H), 0.876 (obsc d, 3H, $J = 6.4$ Hz, C20-H), 0.82 (s, 3H, C16-H). **¹³C-NMR** (100 MHz, CDCl₃): δ 203.0 (C5), 146.8 (C1), 126.6 (C14), 112.8 (C3), 65.1 (C23/24), 64.5 (C23/24), 54.1 (C12), 49.6 (C11), 43.7 (C8), 39.1 (C6), 35.5 (C13), 32.3 (C2), 31.9 (C10), 29.7 (C9), 29.6 (C18), 26.1 (C7), 23.0 (C19), 22.9 (C20), 20.8 (C16), 20.7 (C17). **ESI-MS** m/z (rel int): (pos) 343.1 ([M+Na]⁺, 100). **HRMS** (EI) m/z 321.2431 (M+H⁺), calcd for C₂₀H₃₂O₃ 320.2351.

8 β -(4'-Carboethoxy-3'-ketobutyl)-8 $\alpha,11\beta$ -dimethyl-3,3-ethylenedioxy-12 β -isopropyl-($\Delta^{1,14}$)-hydroazulene 40. In a 100 mL round bottom flask, aldehyde **39** (749 mg, 2.34 mmol, 1.0 equiv) is azeotroped 1 $\times$ from PhH, then SnCl₂ (222 mg, 1.17 mmol, 0.5 equiv), 23.4 mL CH₂Cl₂, and ethyl diazoacetate (295 μ L, 2.80 mmol, 1.2 equiv) are added in succession at rt. The resulting yellow solution evolves N₂ for approx 15 min. After 3.5 h, the mixture is poured into approx 150 mL brine and extracted 3 $\times$ Et₂O. The combined organic extractes are washed 1 $\times$ 1:1 H₂O/brine, 1 $\times$ brine, dried (MgSO₄), filtered, and evaporated to yield the crude β -keto ester **40** as a yellow oil (945 mg, 99%, >95% purity by NMR, no **41** detected). In some cases, varying amounts (15-44%) of dioxolane deprotected β,ζ -diketo ester **41** are also detected. The crude product is generally carried on directly to the next step, but can also be purified by silica flash chromatography (9:1 hexanes/EtOAc, 64%) although separation of **40** and **41** is difficult. **TLC**: R_f 0.48 (plate placed under high vacuum before and after elution; double elution; 4:1 hexanes/EtOAc). **IR** (film): 2951, 1745 (C=O), 1717 (C=O), 1642, 1452, 1367, 1306, 1237, 1164, 1087 (C-O), 1030, 948. **¹H-NMR** (500 MHz, CDCl₃, 85:15 keto/enol form): δ 5.35 (s, 1H, C14-H), 4.21 (q, 2H, $J = 7.1$ Hz, C25-H₂), 4.01 (app q, 1H, $J = 6.0$ Hz, C23/24-H), 3.96 (obsc m, 1H, C23/24-H), 3.92 (obsc app q, 1H, $J = 6.7$ Hz, C23/24-H), 3.87 (obsc app q, 1H, $J = 6.7$ Hz, C23/24-H), 3.47 (app s, 2H, C4-H₂), 2.61 (ddd, 1H, $J = 17.0, 11.7, 5.1$ Hz, C6-H_a), 2.42 (ddd, 1H, $J = 17.0, 11.8, 5.0$ Hz, C6-H_b), 2.35 (obsc d, 1H, $J = 12.9$ Hz, C2-H_a), 2.32 (obsc m, 1H, C13-H_a), 2.18 (d, 1H, $J = 13.5$ Hz, C2-H_b), 1.91 (m, 2H, C7-H_a/C7-H_b/C13-H_b $\times$ 2), 1.83 (obsc dd, 1H, $J = 11.8, 5.2$ Hz, C7-H_a/C7-H_b/C13-H_b), 1.72 (obsc dd, 1H, $J = 15.1, 8.3$ Hz, C10-H_a), 1.70 (obsc m, 1H, C18-H), 1.62 (obsc td, 1H, $J = 9.6, 7.9$ Hz, C12-H), 1.51 (obsc dd, 1H, $J = 15.2, 11.6$ Hz, C9-H_a), 1.30 (obsc m, 1H, C10-H_b), 1.29 (obsc t, 3H, $J = 7.1$ Hz, C26-H₃), 1.09 (dd, 1H, $J = 15.2, 8.4$ Hz, C9-H_b), 0.96 (d, 3H, $J = 6.3$ Hz, C19-H₃), 0.878 (obsc d, 3H, $J = 5.1$ Hz, C20-H₃), 0.873 (obsc s, 3H, C17-H₃), 0.80 (s, 3H, C16-H₃). (*enol form*, diagnostic peaks) δ 12.13 (s, 1H, C5-OH), 5.04 (s, 1H, C4-H). **ESI-MS** m/z (rel int): (pos) 429.2 ([M+Na]⁺, 100); (neg) 405.2 ([M+Cl]⁻, 45).

8 β -(4'-Carboethoxy-3'-ketobutyl)-8 α ,11 β -dimethyl-12 β -isopropyl-($\Delta^{1,14}$)-hydroazulen-3-one **41.** In a 100 mL round bottom flask, the crude dioxolane **40** (943 mg, 2.32 mmol, 1.0 equiv) and TsOH $\cdot$ H₂O (221 mg, 1.16 mmol, 0.5 equiv) are dissolved in 22 mL acetone (reagent grade), then 1.16 mL H₂O (5 vol%) is added and the mixture heated to reflux under a condenser for 90 min. The acetone is evaporated and the residue is taken up in 50 mL Et₂O, washed 1 $\times$ satd aq NaHCO₃, 1 $\times$ H₂O, 1 $\times$ brine, dried (MgSO₄), filtered, and evaporated to yield the crude product as a slightly yellow oil (776 mg). Purification by silica flash chromatography (9:1 hexanes/EtOAc) yields the β,ζ -diketo ester **41** as a clear oil (678 mg, 80% for two steps). **TLC:** *R_f* 0.41 (double eluted; 4:1 hexanes/EtOAc); *R_f* 0.62 (1:1 hexanes/EtOAc). **IR** (film): 2958, 1745 (C=O), 1714 (C=O $\times$ 2), 1462, 1367, 1317, 1259, 1042. **¹H-NMR** (500 MHz, CDCl₃, 94:6 keto/enol form): (*keto form*) δ 5.43 (app t, 1H, *J* = 1.1 Hz, C14-H), 4.19 (q, 2H, *J* = 7.1 Hz, C25-H₂), 3.45 (obsc br d, 1H, *J* = 11.5 Hz, C2-H_a), 3.43 (obsc AB d, 1H, *J* = 15.5 Hz, C4-H_a), 3.39 (obsc AB d, 1H, *J* = 15.5 Hz, C4-H_b), 2.92 (d, 1H, *J* = 11.6 Hz, C2-H_b), 2.54 (ddd, 1H, *J* = 18.2, 9.9, 5.5 Hz, C6-H_a), 2.41 (ddd, 1H, *J* = 18.1, 9.9, 5.5 Hz, C6-H_b), 2.29 (app ddd, 1H, *J* = 15.9, 7.7, 2.7 Hz, C13-H_a), 1.94 (obsc m, 2H, C9-H_a, C13-H_b), 1.90 (obsc m, 2H, C7-H_a, C10-H_a), 1.73 (app ddt, 1H, *J* = 13.0, 9.8, 6.5 Hz, C18-H), 1.66 (ddd, 1H, *J* = 14.4, 9.8, 5.5 Hz, C7-H_b), 1.50 (m, 2H, C9-H_b, C12-H), 1.41 (app dd, 1H, *J* = 14.4, 11.0 Hz, C10-H_b), 1.28 (t, 3H, *J* = 7.1 Hz, C26-H₃), 1.01 (s, 3H, C16-H₃), 1.00 (s, 3H, C17-H₃), 0.97 (d, 3H, *J* = 6.5 Hz, C19-H₃), 0.88 (d, 3H, *J* = 6.6 Hz, C20-H₃). (*enol form*, diagnostic peaks) δ 12.11 (s, 1H, C5-OH), 4.96 (s, 1H, C4-H). **¹³C-NMR** (100 MHz, CDCl₃): (*keto form*) δ 212.0 (C3), 202.3 (C5), 167.1 (C15), 143.2 (C1), 126.6 (C14), 61.4 (C25), 57.9 (br, C12), 49.7 (C8), 49.4 (C4), 49.1 (C11), 42.0 (C2), 37.8 (C6), 36.3 (C10), 35.8 (C13), 32.9 (C7), 32.8 (C9), 29.5 (C18), 23.1 (C19), 22.9 (C20), 20.6 (C16), 17.2 (C17), 14.1 (C26). **ESI-MS** *m/z* (rel int): (pos) 385.1 ([M+Na]⁺, 100); (neg) 397.0 ([M+Cl]⁻, 15), 361.1 ([M-H]⁻, 45). **HRMS** (EI) *m/z* 385.2350 (M+Na⁺), calcd for C₂₂H₃₄O₄ 362.2457

Direct cyclization of β,ζ -diketo ester **41.** In a 25 mL conical flask, NaOEt (21 wt% in EtOH, 0.5 mL) is diluted with 12.9 mL anhyd EtOH (Aldrich SureSeal) to generate a 0.1 N NaOEt solution. This stock solution (364 μ L, 36.4 μ mol, 1.2 equiv) is added to the neat β,ζ -diketo ester **41** (11 mg, 30.3 μ mol, 1.0 equiv) under air in a 4 mL vial. The vial is closed with a teflon-faced cap and the yellow solution is heated to 60 $^{\circ}$ C. After 19 h, the cloudy orange mixture is diluted with 1 N aq HCl and extracted 3 $\times$ EtOAc. The combined organic extracts are washed 1 $\times$ H₂O, 1 $\times$ brine, dried (MgSO₄), filtered, and evaporated to yield the crude product as a yellow oil (11 mg). NMR analysis indicated a 62:30:8 mixture of **44**, **46**, and **45** based on integration of the vinylic C14-H peaks. Purification by silica flash chromatography yielded the "truncated" ester **44** as a clear residue (6 mg), and the tricyclic alcohol **46** as a clear oil (3.5 mg). The tricyclic diketone was isolated from a separate run as a clear residue (0.6 mg).

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8 β -(2'-(Carboethoxy)ethyl)-8 α ,11 β -dimethyl-12 β -isopropyl-($\Delta^{1,14}$)-hydroazulen-3-one 44.

Structure Determination: Inspection of the NMR spectrum revealed that the compound was very similar to **41** but lacked the diagnostic β -keto ester α -protons (C4-H₂). The “truncated” ester structure **44** was confirmed by MS analysis. **TLC:** *R_f* 0.67 (1:1 hexanes/EtOAc). **¹H-NMR** (500 MHz, CDCl₃): δ 5.43 (app s, 1H), 4.11 (q, 1H, *J* = 7.1 Hz), 3.46 (br d, 1H, *J* = 11.6 Hz), 2.94 (d, 1H, *J* = 11.6 Hz), 2.33-2.25 (m, 2H), 2.20-2.12 (m, 2H), 1.98-1.85 (m, 4H), 1.76-1.69 (m, 2H), 1.51 (obsc m, 1H), 1.42 (app dd, 1H, *J* = 15.2, 10.9 Hz), 1.25 (t, 3H, *J* = 7.1 Hz), 1.03 (s, 3H), 1.00 (s, 3H), 0.97 (d, 3H, *J* = 6.5 Hz), 0.88 (d, 3H, *J* = 6.6 Hz). **ESI-MS** *m/z* (rel int): (pos) 343.0 ([M+Na]⁺, 100).

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46. Structure Determination: Inspection of the NMR spectrum at 24 °C revealed several indications of cyclization. Most strikingly, many peaks in the aliphatic methylene region (2.6-1.4 ppm) were broad, consistent with the conformational isomerism reported for guanacastepene A at rt. Furthermore, the diastereotopic ethyl ester methylene protons (C25-H₂), which had exhibited as a single quartet in **41**, now presented as two separate doublets of quartets. The downfield shift of the single vinylic proton from 5.43 ppm in **41** to 6.17 ppm in **46**, together with the absence of the C2-H₂ AB quartet of **41** in the 3.5-2.9 ppm region, supported reconjugation of the double bond with the carbonyl system. Finally, a broad singlet at 4.44 ppm was indicative of a R₂CH-OH group. Presence of a hydroxyl group was confirmed by a broad O-H stretching band in the IR spectrum at 3441 cm⁻¹. We first considered that reduction of the C5 ketone may have occurred, however, the IR spectrum showed two carbonyl C=O stretching bands at 1732 and 1667 cm⁻¹ and MS analysis indicated a molecular weight 16 amu higher than expected for **42**. Thus, we proposed the oxidized structure **46** that was ultimately confirmed by multidimensional NMR analysis at 50 °C. **TLC:** *R_f* 0.25 (1:1 hexanes/EtOAc). **IR** (film): 3441 (br, O-H), 2958, 2932, 2870, 1732 (ester C=O), 1667 (ketone C=O), 1452, 1368, 1297, 1227, 1177, 1021. **¹H-NMR** (500 MHz, CDCl₃): (50 °C) δ 6.17 (d, 1H, *J* = 1.3 Hz, C2-H), 4.43 (br d, 1H, *J* = 6.5 Hz, C14-H), 4.28 (dq, 1H, *J* = 10.8, 7.1 Hz, C25-H_a), 4.21 (dq, 1H, *J* = 10.8, 7.1 Hz, C25-H_b), 2.52 (app dd, 2H, *J* = 7.6, 6.2 Hz, C6-H₂), 2.01 (obsc m, 1H, C7-H_a), 1.97 (obsc m, 2H, C9-H_a, C10-H_a), 1.88-1.77 (obsc m, 4H, C13-H_a, C12-H, C7-H_b, C10-H_b), 1.73 (obsc m, 1H, C13-H_b), 1.65 (obsc app oct, 1H, *J* = 6.7 Hz, C18-H), 1.56 (dd, 1H, *J* = 12.4, 7.4 Hz, C9-H_b), 1.26 (t, 3H, *J* = 7.1 Hz, C26-H₃), 1.24 (s, 3H, C16-H₃), 0.99 (d, 3H, *J* = 6.7 Hz, C19/20-H₃), 0.95 (s, 3H, C17-H₃), 0.92 (d, 3H, *J* = 6.7 Hz, C20/19-H₃). **¹³C-NMR** (100 MHz, CDCl₃): (50 °C) δ 194.3 (C5), 166.5 (C15), 164.1 (C1), 162.0 (C3), 133.3 (C4), 119.3 (C2), 73.6 (C14), 60.9 (C25),

53.2 (br, C12), 48.5 (C11), 38.3 (br, C8), 36.8 (br, C7), 36.7 (C13), 36.4 (C9), 33.8 (C6), 33.5 (br, C10), 28.1 (C18), 25.2 (C16), 23.9 (C19/20), 22.0 (C20/19), 20.5 (br, C17), 14.2 (C26). **ESI-MS** m/z (rel int): (pos) 383.2 ($[M+Na]^+$, 100); (neg) 394.9 ($[M+Cl]^-$, 55), 359.1 ($[M-H]^-$, 40). **HR-FAB-MS** m/z calcd for $C_{22}H_{32}O_4Na$ 383.2198; found 383.2198.

4-Carboethoxy-8 α ,11 β -dimethyl-12 β -isopropyl-14-keto-($\Delta^{1,2},\Delta^{3,4}$)-tricycle **45.** *Structure Determination:* Inspection of the NMR spectrum again indicated cyclization with broad peaks in the aliphatic methylene region (2.6-1.4 ppm) and a complex multiplet corresponding to the ethyl ester methylene (C25-H₂). We noted a further significant downfield shift of the vinylic proton from 6.17 ppm in **46** to 6.87 in **45**, absence of the R₂CH-OH signal around 4.5-4.4 ppm, and the downfield shift of two protons from the 2.1-1.4 ppm range in **46** to 2.2 and 2.5 ppm in **45**. MS analysis indicated a molecular weight 14 amu higher than that expected for **42**. This led us to propose the diketone ester structure **45**, which was confirmed by multidimensional NMR analysis at 24 °C. **TLC:** R_f 0.48 (1:1 hexanes/EtOAc). **¹H-NMR** (500 MHz, CDCl₃, partially assigned based on COSY and NOESY; C7-H₂, C9-H₂, C10-H _{β} not assigned): (**24 °C**) δ 6.87 (s, 1H, C2-H), 4.28 (m, 2H, C25-H₂), 2.57 (obsc m, 2H, C6-H₂), 2.53 (obsc dd, 1H, J = 18.5, 7.7 Hz, C13-H _{α}), 2.18 (dd, 1H, J = 18.6, 12.9 Hz, C13-H _{β}), 2.14-1.95 (br s, 2H), 2.01 (br dd, 1H, J = 12.8, 11.9 Hz, C10-H _{α}), 1.95-1.75 (br s, 2H), 1.80 (app sxt, 1H, J = 6.8 Hz, C18-H), 1.69 (m, 1H, C12-H), 1.60 (obsc m, 1H), 1.27 (t, 3H, J = 7.1 Hz, C26-H₃), 1.22 (s, 3H, C16-H₃), 1.09 (s, 3H, C17-H₃), 1.06 (d, 3H, J = 6.6 Hz, C19-H₃), 0.95 (d, 3H, J = 6.6 Hz, C20-H₃). **ESI-MS** m/z (rel int): (pos) 381.1 ($[M+Na]^+$, 100); (neg) 392.9 ($[M+Cl]^-$, 60), 357.0 ($[M-H]^-$, 65).

ketone 99: Under argon atmosphere, cuprous thiocyanate (2.76 g, 22.5 mmol), powdered 4 Å molecular sieves (3g), and anhydrous diethyl ether (375 ml) were placed in a 500-ml septum-sealed flask equipped with a magnetic stirring bar, and cooled to -45°C. First 29.4 ml (42 mmol) of isopropenyllithium in n-hexane was added by syringe, and the mixture was stirred for 1 h and allowed to warm up to -25°C. Then the mixture was cooled to -60 °C and (S)-2-(methoxymethyl)pyrrolidine (5.67 ml, 45 mmol) in 45 ml of anhydrous ether was added by syringe. Stirring was continued for 30 min while the temperature went up to -50°C. Finally ketone **4** (735 μ l, 7.5 mmol) within 5 min was added by syringe at -100°C and the resulting mixture after stirring for 30 min at that temperature was poured into 80 ml of ice water saturated with ammonium chloride, and 100 ml of ether. After stirring for 15 min the mixture was filtered through Celite. The aqueous layer was separated and washed with 100 ml of ether. The

combined organic layers were washed successively with 50 ml each of 2N HCl, saturated aqueous solutions of sodium hydrogencarbonate and sodium chloride. After drying over magnesium sulfate, the solvent was removed and the reaction mixture was purified by column chromatography to afford ketone **99** was isolated (995 mg, 96 %). Physical properties were identical to those of previous report (Quinkert, G.; Müller, T.; Königer, A.; Schultheis, O.; Sickenberger, B.; Dürner, G. *Tetrahedron Lett.* **1992**, 33, 3469). HPLC analysis showed this product had an ee of 90%. (chiralpak[®] AD, 99.8% hexane:0.2% isopropyl alcohol).

diketone 100: Under argon atmosphere, into a flask were introduced the silyl enol ether of **99** (0.599 g, 2.373 mmol) in dichloromethane at room temperature, then at -20°C, a solution of methyl vinyl ketone (0.162 ml, 1.977 mmol) in dichloromethane, a solution of boron-trifluoride-diethyl ether (25 μ l, 0.1977 mmol) and acetic acid (0.112 ml, 1.997 mmol). The mixture was stirred at -20°C for 1 hr, then allowed to warm to room temperature and saturated aq. NaHCO₃ was added. After extraction with dichloromethane, filtered and evaporated, the reaction mixture was purified by column chromatography to afford the diketone **100** (0.3675 g, 90%). **IR** (thin film) 1720, 1735 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 4.94 (t, 1H, J = 1.5 Hz), 4.76 (s, 1H), 2.65–2.57 (m, 1H), 2.57–2.49 (m, 1H), 2.44–2.37 (m, 1H), 2.37–2.28 (m, 1H), 2.25–2.16 (m, 1H), 2.14 (s, 3H), 2.08–2.00 (m, 1H), 1.96–1.84 (m, 2H), 1.82–1.74 (m, 1H), 1.76 (s, 3H), 0.84 (s, 3H); **¹³C NMR** (100MHz, CDCl₃) δ 222.14, 208.16, 143.90, 113.31, 50.87, 50.27, 38.62, 37.12, 30.38, 29.97, 23.27, 23.19, 18.06; **LRMS** Calcd for C₁₃H₂₀O₂: 208.30. Found: 209.23.

diketone 93: To a benzene solution of **100** (70.5 mg, 0.3384 mmol) was added Pd/C (5 mg) and the reaction mixture was stirred under hydrogen atmosphere. After 2 days, reaction mixture was filtered through a Celite and solvent was removed. The resulting reaction mixture was purified by column chromatography to afford the diketone **93** (65.2 mg, 92%). Identification as *cis* isomer was done as follows: irradiating the 2-methyl gave no nOe effect on 3-H but gave a strong nOe effect on the hydrogen of the isopropyl group. $[\alpha]_D^{24.4} + 5.84$ (c 0.23, CHCl₃); **IR** (thin film) 1720, 1740 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 2.50–2.41 (m, 1H), 2.36–2.28 (m, 1H), 2.26–2.17 (m, 1H), 2.11 (s, 3H), 2.10–2.02 (m, 2H), 1.98–1.91 (m, 1H), 1.80–1.72 (m, 1H), 1.72–1.62 (m, 2H), 1.55–1.40 (m, 1H), 0.99 (d, 3H, J = 6.2 Hz), 0.95–0.90 (m, 6H); **¹³C NMR** (100MHz, CDCl₃) δ 223.8, 208.6, 51.2, 49.7, 39.1, 37.5, 31.4, 30.0, 29.4, 23.5, 22.5, 21.3, 17.8; **LRMS** Calcd for C₁₄H₂₂O₂: 210.31. Found: 210.16.

enone 94: To a diketone **93** (0.296 g, 1.407 mmol) was added a methanolic solution (0.5 M) of sodium methoxide (2 ml). After refluxing overnight, saturated aq. NaCl was added. The mixture was extracted with diethyl ether, the combined organic layers were washed with brine, and then the solvent was evaporated. The reaction mixture was purified by column chromatography to afford **94** (0.265 g, 98%). $[\alpha]_D^{22.6} + 62.9$ (c 1.0, CDCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.74 (s, 1H), 2.68–2.56 (m, 1H), 2.56–2.47 (m, 1H), 2.47–2.38 (m, 1H), 2.38–2.27 (m, 1H), 2.27–2.20 (m, 1H), 2.05–1.96 (m, 1H), 1.89–1.79 (m, 1H), 1.73–1.64 (m, 1H), 1.62–1.48 (m, 1H), 1.35–1.25 (m, 1H), 1.04 (s, 3H), 1.00 (d, 3H, $J = 6.6$ Hz), 0.95 (d, 3H, $J = 6.6$ Hz); $^{13}\text{C NMR}$ (100MHz, CDCl_3) δ 199.67, 180.53, 121.20, 58.03, 45.4, 37.5, 34.0, 30.3, 29.4, 27.5, 23.4, 23.0, 16.8; **HRMS** Calcd for $\text{C}_{13}\text{H}_{20}\text{O}$: 192.30. Found: 192.1516.

dienone 98: To a solution of $(^i\text{Pr})_2\text{NH}$ (0.53 ml, 3.786 mmol) in THF was added $n\text{-BuLi}$ (1.6 M Hexane, 2.11 ml, 3.380 mmol) at -78°C . After 30 min at 0°C , the reaction mixture was cooled to -78°C and a THF solution of **94** (0.26 g, 1.352 mmol) was added with stirring. After 30 min, TMSCl (1 M THF, 2.7 ml, 2.70 mmol) was added, the cold mixture was stirred for 30 min, then warmed to room temperature and submitted to an aqueous workup. After evaporation *in vacuo*, the crude diene **95** was diluted with diethyl ether and cooled to 0°C . Diethyl zinc (1.9 ml., 1.864 mmol) and diiodomethane (0.11 ml, 1.367 mmol) were successively added and the reaction mixture was warmed to room temperature. After being stirred overnight, the reaction mixture was cooled in an ice-water bath and quenched with ammonium chloride. After separation, the ether layer was filtered through a short pad of silica gel, which was washed with 20:1 (v:v) ether-pentane. The combined filtrates were washed with ammonium chloride and brine. After evaporation *in vacuo*, the crude trimethylsilyloxycyclopropane **96** was diluted with DMF. To this was added, via syringe pump during 2 hr, a solution of FeCl_3 in DMF, previously prepared by slowly adding anhydrous FeCl_3 (0.548 mg, 3.380 mmol), with stirring, to DMF precooled at 0°C . After the addition was complete, the resulting brown solution was stirred at room temperature for 2 more hours, then quenched with ice-cold 1N HCl. After aqueous workup and evaporation *in vacuo*, the crude chlorocycloheptenone **97** was dissolved in methanol saturated with NaOAc (5 ml) and heated at reflux for overnight. The reaction mixture was cooled to room temperature and submitted to aqueous workup. After evaporation of organic solvent, the crude

product was purified by column chromatography to afford **98** (110.5 mg, 40%). $[\alpha]_D^{22.7} - 65.6$ (c 0.35, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.42 (m, 1H), 6.13 (m, 1H), 5.97 (d, 1H, $J = 1.9$ Hz), 2.72 (m, 1H), 2.64–2.45 (m, 3H), 1.96–1.86 (m, 1H), 1.75–1.67 (m, 1H), 1.56–1.47 (m, 2H), 1.09 (s, 3H), 1.03 (d, 3H, $J = 6.7$ Hz), 0.95 (d, 3H, $J = 6.7$ Hz); $^{13}\text{C NMR}$ (100MHz, CDCl_3) δ 191.13, 173.20, 140.83, 133.61, 124.78, 58.32, 48.32, 39.07, 32.92, 28.15, 26.61, 24.10, 22.42, 17.74; **HRMS** Calcd for $\text{C}_{14}\text{H}_{20}\text{O}$: 204.31. Found: 205.159.

27¹³C NMR (500 MHz, CDCl₃)

S64

60

 ^1H NMR (400 MHz, CDCl_3)

24

Compound 100

Compound 93

Compound 94

Compound 98

X-Ray Structure of 73

The structure of **73** has been determined by a single-crystal X-ray analysis. In the crystal, the methyl group C-20 is disordered. Perspective drawings of Rotamer A (approximately 75% occupancy) and Rotamer B (approximately 25% occupancy) of **73** are shown in the Figures 1 and 2. The hydroxyl group of a molecule of **73** forms an intermolecular hydrogen bonds with the carbonyl oxygen.

73
(racemic)

The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu $K\alpha$ radiation, ω - 2θ scans). The size of the crystal used for data collection was approximately 0.44 x 0.56 x 0.88 mm. The data were not corrected for absorption. Of the 3150 independent reflections for $\theta < 60^\circ$, 2053 were considered observed [$I > 3.0\sigma(I)$].

The structure was solved by a multiple-solution procedure¹ and was refined by full-matrix least squares. In the final refinement, the nonhydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure-factor calculations, but their parameters were not refined. The final discrepancy indices are $R = 0.0610$ and $R_w = 0.0669$ for the 2053 observed reflections. The final difference map has no peaks greater than $\pm 0.22 \text{ e } \text{\AA}^{-3}$. The X-ray data are summarized in Tables I to VI.

1. P. Main, S. Fiske, S. Hull, L. Lessinger, G. Germain, J. P. Declercq, M. Woolfson, (1982). MULTAN 11/82. University of York, England and University of Louvain, Belgium.

Figure 1. X-ray structure of Rotamer A (approximately 75% occupancy) of **73** at 295 K

Figure 2. X-ray structure of Rotamer B (approximately 25% occupancy) of **73** at 295 K